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Multi-centre ethics and research governance review can impede non-interventional clinical research

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TITLE: Multi-Centre Ethics and Research Governance Review Can Impede Non-Interventional Clinical Research

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ABSTRACT

Background: The Inter-jurisdictional National Mutual Acceptance (NMA) scheme for Human Research Ethics Committee (HREC) approvals of human research is designed to reduce the reported delays and costs of ethical review. Introduction of the NMA set forth an uncoupling of the ethics and governance review processes, permitting a single ethical review for multiple sites, whilst continuing separate governance review for each centre covering financial and operational aspects of the research project.

Aim: Compare the time required to gain ethics and governance approvals in Australia for a non-interventional investigator-led study from December 2015, to approval times for an earlier pre-NMA study utilising a similar study design and study sites, and evaluate the effect that the NMA has had on total approval time for non-interventional multi-centre projects.

Methods: We recorded the time taken to obtain ethics and governance approval at 16 sites for our nationwide low-risk non-interventional study looking at the prevalence and aetiology of non-tuberculous mycobacterial infection in people with cystic fibrosis (CF) in Australia.

Results: Applications were submitted to three hospital and one university HREC to conduct our study at 16 hospital sites, HREC approval took from 16 – 79 days (median 28). Subsequent site-specific governance approval at 15 hospital sites took 23 – 225 days

(median 83). The entire process of gaining ethical and governance approval to conduct the study at 16 sites took 24 months at an estimated cost of \$AUD56000 (\$USD 42000).

Conclusions: Lengthy governance approval processes negate benefits gained from centralised ethics review under the NMA.

KEY WORDS

Multi-centre, governance, human research ethics committee

ABBREVIATIONS

CF, Cystic Fibrosis; **HoMER**, Harmonisation of Multi-Centre Ethical Review (HoMER)
HREC, Human Research Ethics Committee; **MRI**, Medical Research Institute; **NHMRC**, National Health and Medical Research Council; **NMA**, National Mutual Acceptance Scheme; **NTM**, Nontuberculous mycobacteria; **RGO**, Research Governance Office; **SSA**, Site-specific Assessment

INTRODUCTION:

Research ethics and governance processes are core to ensuring that research is ethical, feasible and meets all relevant regulatory and legislative requirements. In the context of multi-centre research, complicated approval processes have led to increased costs and time

restraints for researchers.¹⁻¹² During the past decade, the process for gaining multi-centre ethics approval in Australia has been overhauled to improve efficiency, minimise duplication and reduce approval times and costs. In 2007, the Harmonisation of Multi-Centre Ethical Review (HoMER) project was introduced¹³, whereby a multi-centre study could undergo a single ethical review by a certified lead Human Research Ethics Committee (HREC), which would then be accepted by other HRECs within the same jurisdiction. Queensland, New South Wales and Victoria began the Inter-jurisdictional National Mutual Acceptance (NMA) of ethical and scientific review of clinical trials in 2011. South Australia joined in 2013. In December 2015, the scope of the NMA was expanded beyond clinical trials to include all human research, thus streamlining the process for non-clinical trial multi-site research. Subsequently, the Australian Capital Territory (2016) and Western Australia (2017) joined the NMA.¹⁴ The NMA uncoupled the process of ethical review from institutional governance assessment of the resource, financial, operational and contractual aspects of research, including negotiation of an agreement. Site-specific assessments (SSA) which have formed part of governance approval in some jurisdictions since 2009, are required for each hospital site, even for those projects ethically approved as being low-to-negligible risk.

Recent evidence suggests that the process of ethics review harmonisation has shifted the delays and duplication from the HREC application process to the governance approval process.^{7, 15} In 2009, we reported the overall time and resource implications of HREC review for a National Health and Medical Research Council (NHMRC)-funded low-risk

non-interventional multi-centre study in Australia.⁴ In December 2015, we commenced the process of applying for ethics and governance approval to conduct another multi-centre study utilising the same sites and a similar low-risk non-interventional design as the previous study. By comparing the approvals process for the two similar studies, conducted pre- and post- NMA, we were uniquely placed to analyse the effect the NMA scheme has had on the time and resources required to acquire approvals for a multi-centre research.

METHODS:

The approved project is a longitudinal study investigating the clinical implications of, and risk factors for, the acquisition of nontuberculous mycobacteria (NTM) infection in cystic fibrosis (CF) patients (NTM in CF study). Investigators at 20 CF clinics within 16 Australian hospitals recruit patients, collect clinical samples (as a part of routine clinical practice) and provide clinical data for four years. The study leverages off clinical practice, participants are required to answer a short questionnaire at their routine clinic visit (recruitment, 6 months and then annually). Sites receive a small payment per recruit. Funding for the study was granted by the NHMRC in September 2015 and is administered by QIMR Berghofer Medical Research Institute, Brisbane, Australia. Ethics and governance applications occurred between November 2015 and November 2017.

HREC approvals were sought under the NMA scheme (HREC/15/QRCH//247; HREC/15/WCHN/193; 2016018EP; H0015622). As the study involves recruitment of paediatric patients a standard risk National Ethics Application Form was submitted to a children's hospital HREC in each jurisdiction. The duration of review was calculated from

the HREC submission closing date to the approval dates on the HREC approval letter (inclusive). When further information was requested, replies were supplied within three days.

SSA applications were submitted via the Australia Online Forms for Research website¹⁶ for 13 centres, except for Western Australian sites where a state specific SSA form was required. All 15 sites required the negotiation of a study-specific agreement between the Medical Research Institute (MRI) administering the grant and the site. The agreement was drawn up by Grants administration and Legal teams of the MRI in consultation with the legal team of the Metro North Hospital and Health Service, Brisbane, Australia.. SSA approval times were calculated as the time from receipt acknowledgement by the Research Governance Office (RGO) to the date of issue of the approval letter. If the approval/signature period spanned the Christmas/New year period two weeks were subtracted from the calculated time interval. The approval time has been broken down into duration of review by the RGO and duration of review by the MRI. One centre required a finance and administration form to be submitted to the University HREC in lieu of a SSA. The median total time was calculated taking into consideration the review time spent with the HREC plus the duration of governance review at each individual site and excludes time taken to draw up contracts.

Statistical comparisons were made using unpaired t-tests in Graphpad Prism V7.02. When the sample sizes and variances of compared groups were disparate, Welch's correction was applied.

RESULTS:

HREC applications were required in four regulatory jurisdictions. Approval from the lead HREC in Queensland was recognised by all hospital sites in Queensland (n=4), New South Wales (n=4) and Victoria (n=3). Approval by the lead HREC in South Australia and Western Australia was recognised by the second site in both states. Tasmania allowed the submission of a state-specific prior ethical approval form to the University of Tasmania HREC (Table 1).

The median duration of review of the HREC applications was 28 days (range 16 – 79) (figure 1). Two HRECs approved the project as submitted with no revision, two HRECs required minor revision of the Patient Informed Consent Forms (PICF) and minor revisions to the protocol in regards to risk management and data security.

Fifteen individual site-specific governance approvals were required. It took a median of 83 days (range 34 to 225) from SSA submission to RGO approval. Time to negotiate legal agreements between the MRI and each hospital site was highly variable and caused delays in the governance approval process. Seven sites signed the submitted contract without negotiation, these seven sites had a median SSA approval time of 49 days (range 23 to 70). Eight sites requiring legal negotiation had a median SSA approval time of 158 days (range 83 to 225). Both the RGO and the the MRI contributed to delays in project approval during the contract negotiation process (Figure 1). The median time in the hands of the RGO was

49 days (8 – 170) and the median time in the hands of the MRI was 31 days (range 5 – 96) ($p>0.05$). , The median total time that applications spent under review (ethics and governance combined) was 99 days (range 39 – 241) (Figure 1).

In Tasmania, in lieu of an SSA, a Finance and Administration form was submitted to the University HREC. In this instance the site had no specific requirement for a study agreement, but the MRI administering the NHMRC grant requested a signed agreement. Contract revision and signing by personnel in the Tasmanian Health Service led to an approval time of 303 days. As this was not part of a formal SSA approval process, this value has not been included in the calculation of SSA approval times.

During SSA preparation and review, a total of eight amendments were made to the original lead HREC approval at the request of reviewing governance officers or site PIs. At each site, we were required to submit an average of 32 supporting documents (range 18 – 45). The SSA had to be finalised and submitted online prior to signing, however, signature collection delayed final submission of the hard copy SSA to the RGO by several weeks. It took a median of 27 days (range 2 – 98) to collect up to seven original signatures on the SSA (Table 1).

The entire process of gaining the appropriate ethics and governance approvals for the study took 24 months. HREC applications began in November 2015 and all sites were approved by April 2016 (~6 months). Preparation of the study agreement began in February 2016 and was completed in June 2016 (~4 months). SSA applications were submitted between June 2016 and May 2017, with the final site approved in November 2017 (~17 months). In

total, it is estimated that 4600 pages and seven months full-time equivalent of a Research Officer's time at a cost of ~\$56000 AUD (~\$42000 USD) was expended. Due to the protracted process of gaining multiple site approvals, our funded 5-year longitudinal study is likely to limit sample collection to four years.

DISCUSSION:

The introduction of the NMA to the HREC approval framework has allowed inter-jurisdictional acceptance of approval from a lead HREC, but has decoupled ethics and governance review processes. We previously conducted a non-interventional research project looking at *Pseudomonas aeruginosa* epidemiology in CF clinics in Australia (ACPinCF). The approval application process occurred in 2007-2008.⁴ Our current study looking at the epidemiology of NTM in adult and paediatric CF clinics in Australia (NTM in CF study) commenced in December 2015. The two studies share a similar design and protocol, are non-interventional, leverage off clinical practice, and involve most of the same hospitals. Comparison of the approval requirements and times for these two very similar studies, conducted pre- and post-NMA, shows that the introduction of the NMA has increased the time taken for approval of non-interventional research. In the earlier ACPinCF study it took a median 46 days (range 13-77) for combined ethics and governance approval to be granted. For the current NTM in CF study, the median total approval time for each site was 99 days (range 39 – 241). Our study is not alone in highlighting the heterogeneity of approval times and showing that the time taken to obtain

site governance approval of low risk non-interventional research exceeds the time taken to have the project ethically approved.^{7, 15, 17}

The introduction of the NMA has clearly reduced the time taken to receive ethics approval, the time and effort spent on duplicative administrative tasks in preparing applications and the amount of paper required in the approval process (~ 35% of that used in the ACPinCF study). However, the centralised HREC review process has not reduced the time taken for study approval at sites. Any improvement in HREC approval times is now negated by the complex and lengthy governance approval process.

Impediments to and solutions for timely governance review

The requirement to submit a unique study agreement for a non-interventional study is the major impediment to timely governance review of non-interventional clinical research. In our study, all sites that accepted the study agreement without alteration were approved by the RGO in <60 days. When negotiation of study contracts was required only 3 of 8 applications were approved in <60 days. For clinical trials, Medicines Australia has developed standardised templates for agreements and indemnities¹⁸, these are generally accepted by all RGOs and their introduction has significantly minimised legal review requirements and improved governance approval times for clinical trials. However, as there are no specific templates for investigator-led non-interventional clinical research, for each study a unique agreement must be negotiated reflecting the specific scope, purpose

and arrangements of the research project across a number of areas such as intellectual property (IP); project funding; confidentiality and copyright; data management; responsibility for ethics and research governance approval; handling of disputes and dispute resolution; reporting obligations and state-specific legislation. Clinical (yet non-interventional) research needs the suite of standard clinical research agreements broadened to encompass collaborative non-interventional clinical research. Standard template agreements would greatly reduce the time and costs associated with lengthy preparation and legal review of agreements. We are not alone in making this suggestion^{12, 19} and we believe this would be rapidly embraced by researchers. Furthermore, the time spent negotiating legal agreements should be commensurate with the level of risk and/or anticipated IP gain; unnecessary time and publically-funded grant support is required to negotiate agreements often where there is little risk and/or no realisable IP. Not all delays are due to RGO handling of agreements. The MRI overseeing the funding for this study took 4 months to draw up study agreements and in 4 of the 8 instances where the legal agreement required negotiation, the days in review with the MRI exceeded the days in review by the RGO. A standardised agreement template would assist to reduce delays, and would be welcomed by both RGOs and researchers. Recently, a working committee developed conditions and clauses adapting the Medicines Australia Clinical Trials Research agreement for use in approvals related to clinical registries. These clauses have been recognised and routinely accepted by sites from multiple state jurisdictions participating in the working group and provided an example of an approach that could be applied nationally to reduce the burden of agreement development and negotiation.¹⁹ A

working committee to discuss application of the standard templates to non-interventional research would require the input of RGOs, lawyers and hospital administrators as well as experienced researchers and MRI representatives.

Greater consistency and reduced duplication of the necessary documentation, both across and within state jurisdictions, is warranted. Obtaining duplicative signatures, reformatting of documents to various different site requirements and repetitive uploading is neither time nor cost-effective.^{2, 12, 17, 19} Clay-Williams *et al.* (2018) recently proposed a framework encompassing a single ethics and governance review process recognised by all Australian states to increase efficiency and decrease approval times.¹² A centralised system for both HREC and governance review has been in place in the UK since 2016. The Health Research Authority (HRA) approval system, comprises a centralised assessment of study compliance with applicable regulations and standards, and replaces the need for local review by each participating site and has a benchmark of 70 calendar days for review of applications.²⁰ Where required, HRA coordinates ethical review by independent HRECs. There are currently no published data about the effectiveness of the UK system. Given that Australian health departments are under state jurisdiction, implementation of a nationalised governance review process may not be feasible without legislation changes and the development of specific infrastructure. Given the NMA rollout commenced with the HoMER project in 2007 and took eight years to encompass non-interventional clinical research, such a solution is unlikely to be implemented in the foreseeable future. Foot *et al.*, (2018) have suggested a Local Health Network (LHN) level governance process,

where a lead RGO would assess an application on behalf of all hospitals in the network. Unfortunately, only two of our 15 participating hospitals fell within the same LHN. An SSA application for the first hospital site was approved in 49 days and the SSA application for a second site within the same network was approved in just 23 days. So whilst this approach will improve approval times at a local level, the effect may not be realisable on a larger scale for multi-centre studies. A simple approach to aid in consistency and accessibility of information would be to establish a 'one-stop shop', a central national or state-wide website hosting all HREC and LHN governance requirements, specific forms, guidance and closing dates for all of the jurisdictions. Furthermore, the introduction of a national ethics and governance system for uploading of documentation supporting ethics and SSA applications, would be welcomed by researchers.

Only a few Australian jurisdictions have introduced benchmarks for duration of governance review.²¹ These benchmarks represent the time from the date of a valid submission to the date of final approval. They do not encompass the additional time taken before an application is made valid, which may, such as in our study include substantial time due to contract negotiations. There is limited accountability of the extent of adherence to benchmarks. Interestingly, as of Quarter 1 2018-2019 the HRA system of the United Kingdom will move away from using a 70 day benchmark for combined ethics and governance approval, instead focusing on transparency, accuracy and meeting sponsor expectations.²² The pharmaceutical industry is seeking a combined 30-days ethics and governance review time frame. With standard templates, a clinical trial can be approved in

as little as a week. However, the contracting for non-commercial studies is more difficult and applications are generally not as well-prepared. We need a uniform, simplified national system with approved templates for site specific applications and contracts which will cover the large majority of studies.

Whilst enhancing Australia's clinical trial capacity is a national priority,²³ options for reform should not be limited to clinical trials as timely approval is important for all types of research activities. The Queensland health department is currently trialling a simplified research governance approval process for studies that are considered low cost/low risk. Stratifying the SSA process according to risk is a positive step but initiatives are still required for research that sits between the spectrum of low cost/low risk and a clinical trial.

Suggestions for researchers

Researchers applying for funding for multi-centre studies need to ensure they consider the budgetary implications to support ethics and governance applications. The inclusion of salary for a study coordinator in the budget for our current study was questioned by an NHMRC grant assessor. However, our experience with this study has proven the worth of budgeting for a dedicated and skilled coordinator to follow-up with each HREC and RGO. The timeline of research takes into consideration the time consuming process of gaining approval, otherwise longitudinal studies may be bereft of funding before key time-points are achieved..¹²

CONCLUSION

Implementation of a centralised HREC review process has not reduced the time taken for study approval at sites. While centralising ethics and governance is an attractive proposition for researchers, implementation of a national review system may not be feasible and is unlikely to offer a solution in the short term. To improve approval times in the foreseeable future, we advocate for the establishment of standardised agreements for non-interventional studies. We also propose the SSA review process be stratified according to relative risk of the project, aiming to encompass projects that currently fall within the no man's land between low/negligible risk projects and clinical trials. Lengthy legal review and approval time leads to an increase in research costs and a delay in commencement which translates into delays in producing research data that can lead to improvements in patient care. The costly delays and lack of cohesion in the current system is a significant impediment to multi-centre research in Australia.

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applications. CD and TC have no disclosures. SCB is a site principal investigator, advisory board member, and writing group member; he has received travel support from Vertex Pharmaceuticals Incorporated to attend investigator meetings. He also has been a site principal investigator, and received travel support from Galapagos and Flatley to attend investigator meetings and attended advisory board meetings for Abbvie/Galapagos. He has received travel support to participate in conference symposia from Novartis, Gilead and Galapagos.

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Table 1: Timelines of applying for ethics and governance approvals for the National NTM in CF Study.

Process	Type of application	Number of applications	Median (range) number of signatures	Median (range) number of documents submitted	Median (range) days to collect signatures	Median (range) days from submission to approval*
Ethics approval	Standard Risk	4	NA	21 (19-22)	NA	28 (16-79)
	Prior Approval Form	1	3	22	10	25
Governance	SSA	15	4 (2-7)	30 (18 – 47)	27 (2 – 98)	83 (34 – 225)
	Finance and Administration form	1	1	9	7	303

NA, not applicable, 31 signatures required on the NEAF but signatures only collected once as the same set of signatures were submitted to each HREC; SSA, site specific assessment. * Including negotiation of study agreements.

Figure 1: Duration of application review (in days). Black bars represent the duration of review of HREC applications (denoted HREC with state of inter/intra-jurisdiction recognition of approval indicated by a letter). White and grey bars represent the duration of review of SSA applications; white, time in review with the research governance office; grey, time the application spent in review and collecting signatures at the Medical Research Institute; *sites where study agreements required negotiation; #Letter denotes different Australian states; ~Number denotes individual sites within each state.

HREC-A[#] BC
 HREC-D
 HREC-E
 HREC-F
 A[#] 1
 A2
 A3
 A4
 B1
 B2
 B3
 B4
 C1
 C2
 C3
 D1
 D2
 E1
 E2

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ABSTRACT

Background: The Inter-jurisdictional National Mutual Acceptance (NMA) scheme for Human Research Ethics Committee (HREC) approvals of human research is designed to reduce the reported delays and costs of ethical review. Introduction of the NMA set forth an uncoupling of the ethics and governance review processes, permitting a single ethical review for multiple sites, whilst continuing separate governance review for each centre covering financial and operational aspects of the research project.

Aim: Compare the time required to gain ethics and governance approvals in Australia for a non-interventional investigator-led study from December 2015, to approval times for an earlier pre-NMA study utilising a similar study design and study sites, and evaluate the effect that the NMA has had on total approval time for non-interventional multi-centre projects.

Methods: We recorded the time taken to obtain ethics and governance approval at 16 sites for our nationwide low-risk non-interventional study looking at the prevalence and aetiology of non-tuberculous mycobacterial infection in people with cystic fibrosis (CF) in Australia.

Results: Applications were submitted to three hospital and one university HREC to conduct our study at 16 hospital sites, HREC approval took from 16 – 79 days (median 28). Subsequent site-specific governance approval at 15 hospital sites took 23 – 225 days (median 83). The entire process of gaining ethical and governance approval to conduct the study at 16 sites took 24 months at an estimated cost of \$AUD56000 (\$USD 42000).

Conclusions: Lengthy governance approval processes negate benefits gained from centralised ethics review under the NMA.

KEY WORDS

Multi-centre, governance, human research ethics committee

ABBREVIATIONS

CF, Cystic Fibrosis; **HoMER**, Harmonisation of Multi-Centre Ethical Review (HoMER)
HREC, Human Research Ethics Committee; **MRI**, Medical Research Institute; **NHMRC**, National Health and Medical Research Council; **NMA**, National Mutual Acceptance Scheme; **NTM**, Nontuberculous mycobacteria; **RGO**, Research Governance Office; **SSA**, Site-specific Assessment